CoQ_{10}-containing preliposomes and preparation thereof

Field Of The Invention

The present invention relates to field of Pharmaceutics and cosmetic, specially, relates to CoQ_{10}-containing preliposomes, in particular, relates to the preparation method and the application of CoQ_{10}-containing preliposomes which contains spongiamine.

BACKGROUND Of The Invention

CoQ_{10} (conenzymeQ_{10}, ubidecarenone) is a kind of liposoluble quinine compound, which has the same character with vitamin. The prominence function of CoQ_{10} is anti-oxidation and to clean the free radicals, CoQ_{10} is one of the most important functional components used in many anti-aging products at present. It is proved by the experiment that CoQ_{10} can accelerate the metabolism of the skin, accelerate the transport of cellular respiration chain and the ATP production of the skin of face and hand. Simultaneity, CoQ_{10} can inhibit the peroxide of the skin lipid, consequently nourish and activate the skin. It is reported that the body slimming lotion and UV expert cream which contains CoQ_{10} has obvious effect on preventing the furrows, whitening the complexion, increaseing the elasticity of the skin and so on. CoQ_{10} not only protect the skin, but also prevent and cure the skin diseases of the human being. It is proved by the experiment that CoQ_{10} has obvious therapeutic effect on

photoallergy, dermatitis, hair-lose, bedsore, ulcer and woundof the skin, hyperpigmentation and so on. As the molecular structure of CoQ_{10} has an unsaturated double bond, CoQ_{10} is extremely unstable and is easy to be oxidated and decomposed by the oxygen and light in the air, and heating or contacting with metal ion will accelerate it to be decomposed. As a result, the content of CoQ_{10} in the product has decreased, or the activity of CoQ_{10} lost quickly, then affect the quality and actual effect of the product. In addition, CoQ_{10} is a liposoluble compound, which will result in difficulty in mixing with the water-solubility cosmetic. The foregoing disadvantages of CoQ_{10} extremely restrict the development and application of CoQ_{10}.

Liposome is composed by hydrophilic bursa bubble which consists with lecithoid double molecular layer. Liposome has the character to improve the stability of drug encapsulation, facilitate the percutaneous absorption of the drug, prolong the time of drug action, control the drug targeting at the local pathological changes part of the body, and decrease the side effect of the drug. Thus, as drug carrier, liposome has been widely used in Pharmaceutics and cosmetic. CoQ_{10} liposomes could improve the stability of the drug, facilitate the percutaneous absorption of the drug, and increase the water-solubility of the drug. But generally being a kind of liposomes suspension solution, CoQ_{10} has obvious shortcomings in the stability. The reasons are as following:

1. As colloid particulate, liposome is a kind of thermodynamics instability system, which is easy to congregate, fuse and sedimentate, the oxidation decompose of the lecithoid, leakage of the encapsulation drug in the water, etc., will result in the instability of the liposome.
2. The instability of the structure of CoQ_{10} will make the drug more instable in the water.
3. The ratio of CoQ_{10}, liposome suspension and the drug content is generally fixed; however, the required content of CoQ_{10} differs in different cosmetics. Thus, it is not convenient to mix CoQ_{10} liposome suspension with cosmetic which contains CoQ_{10}.

So it is necessary to find a kind of liposome prescription which is convenient, flexible, easy to mix with cosmetic which contains CoQ_{10}, able to make the liposome and drug more stable, and able to be stored for a long time.

The description of the invention

The object of present invention is to overcome the shortcomings of CoQ_{10} and common CoQ_{10} liposome, and to supply a kind of CoQ_{10} –containing preliposomes which contains spongiamine. The present invention could increase the stability of CoQ_{10} and liposome and make the cosmetics mixing more flexible and convenient.

CoQ_{10} –containing preliposomes made by present invention are a kind

of solid preparation which are the granular and lyophilized, before using, water is added to the CoQ_{10} –containing preliposomes, after hydration and surging, CoQ_{10} –containing preliposomes could become CoQ_{10} –containing liposomes.

The structure of the CoQ_{10} –containing preliposomes mentioned in present invention contains spongiamine with the concentration at 0.1% ~ 20% (W/W). Spongiamine can further facilitate the percutaneous absorption and improve the effect of CoQ_{10} in the cosmetic.

The CoQ_{10} –containing preliposomes which contain spongiamine mentioned in present invention are prepared by the following method and process:

1) CoQ_{10}, spongiamine and other lipid component melted by heating or dissolved by proper organic solvent, and lipid solution is made,
2) Use fluidized bed, make the above-mentioned lipid solution sprayed on the underlay which is suspended in the middle of the fluidized bed, let the organic solvent volatilized, and CoQ_{10} –containing preliposomes which contain spongiamine are got,
3) Make the lipid solution mentioned in step 1) and water solution which contains underlay by known methods such as membrane disperse method or melt method or infuse method, and CoQ_{10} –containing liposomes which contains underlay aregot,

4) Make the CoQ_{10}–containing liposomes which contains underlay freeze drying or spray drying, wipe off the moisture, CoQ_{10} –containing preliposomes which contains spongiamine are got.

The CoQ_{10}–containing preliposomes mentioned in present invention contains CoQ_{10} with the concentration at 0.2 ~ 40% (W/W), after restoring by adding water, the concentration of CoQ_{10} is at 0.1 ~ 20% (W/W).

The proper organic solvents mentioned in present invention include dichloromethane, trichloromethane, ether and ethanol.

The concentration of underlay mentioned in present invention involved in the CoQ_{10} preliposomes which contains spongiamine is 1~80%.

The underlay mentioned in present invention is selected from one of the following materials: mannitol, glucose, sorbitol, sucrose, lactose, fucose, sodium chloride and polyvinylpyrrolidone.

The lipid component mentioned in present invention include spongiamine and at least one of the following components: cholesterol, soy lecithin, yolk lecithin, hydrogenated lecithin, DSPC, DPPP, poloxamer, DMPC and non-ionic surfactant like Brij.

The materials used in present invention are all bought from the market.

The CoQ_{10} –containing preliposomes which contains spongiamine

mentioned in present invention not only have the same merit as the common liposomes, for example, increase the stability of the drug, facilitate the percutaneous absorption of the drug, prolong the time of drug action, but also have the following merits:

1. Increase the stability of CoQ_{10} –containing liposomes, can be stored for a long time.

Because the above mentioned preliposomes are solid drug, it can overcome the shortcomings that the common liposomes have, such as congregate, sedimentate, fuse, and leakage and so on.

2. Increase the stability of the CoQ_{10}.

Because the above mentioned preliposomes are solid drug, it could make the unstable drug more stable in the solid state than in the liquid state.

3. Facilitate the percutaneous absorption of the CoQ_{10}.

Because the structure of the above mentioned liposomes contain spongiamine, it could obviously facilitate the percutaneous absorption of the drug.

4. Can be mixed with other components at random; make it easier and more convenient to confect the cosmetic which contains CoQ_{10}.

Generally, for the cosmetic which contains liposome, there is a certain range of the liposome volume. If the contains of liposomes exceed the

range, the character of the cosmetic will be affected, such as viscosity, flow property, viscosity, the content of the active component and so on, furthermore, it is different for the required content of CoQ_{10} for certain cosmetic. Before use, water can be added to the CoQ_{10} –containing preliposomes which contains spongiamine mentioned in present invention on demand, so liposomes which have different content of drug can be got to meet different cosmetic prescription.

Examples

Example 1:

Get 120g of CoQ_{10}, 50g of spongiamine, 50g of yolk lecithin, 100g of cholesterol, 100g of sucrose, add PBS (pH 7.4) to the volume of 1000 ml.

Put CoQ_{10}, spongiamine, yolk lecithin and cholesterol from the above prescription into a triangle flask, heat to fusion, store in water bath at 80 ℃ for further use. Use 800 ml of PBS (pH 7.4) to dissolve the above mentioned 140g of sucrose, filter, heat the filter solution in water bath to reach the same temperature with the liposomes solution, mix the water solution with liposomes solution by surging, then cool, add PBS (pH 7.4) to get 1000 ml of mixed solution, after high pressure homogeneous management (50 MPa of high pressure, 10 MPa of low pressure), liposomes suspension solution is got, after spray drying, a kind of well fluid CoQ_{10} –containing preliposomes which contains spongiamine is got.

Example 2:

Get 30g of CoQ_{10}, 50g of spongiamine, 30g of soy lecithin, 100g of cholesterol, 40g of poloxamer F_{68}, 200g of glucose, 200 ml of chloral, add PBS (pH 7.4) to the volume of 1000 ml.

Put CoQ_{10}, spongiamine, soy lecithin, poloxamer F_{68} and cholesterol from the above prescription into a 1000 ml ofrockered flask, use chloral to dissolve the lipid components, rotary membrane evaporate in water bath at 25~40 ℃ to make the lipid form a layer of membrane at the bottom of the rockered flask for further use. Use 800 ml of PBS (pH 7.4) to dissolve the above mentioned 200g of glucose, filter, put the filter into the above mentioned flask, hydrating and surging, add PBS (pH 7.4) to get 1000 ml of mixed solution, after ultrasonic treatment (output 4, duty cycle 50%, time 10 mins), liposomes suspension solution is got, after freeze drying (temperature at -50℃, the degree of vacuum is 50 millitorr), a kind of loose CoQ_{10} –containing preliposomes which contains spongiamine is got.

Example 3:

Get 50g of CoQ_{10}, 50g of spongiamine, 60g of hydrogenated lecithin, 40g of cholesterol, 50g of poloxamer F_{68}, 80g of fucose, 200ml of ether, add PBS (pH 7.4) to the volume of 1000 ml.

Put CoQ_{10}, spongiamine, hydrogenated lecithin, poloxamer F_{68} and cholesterol from the above prescription into a 500ml of triangle flask, use

ether to dissolve the lipid components for further use. Use 800 ml of PBS (pH 7.4) to dissolve the above mentioned 80g of fucose, filter, put the filter into a triangle flask, store in water bath at 30~60℃, mixing round by magnetic force at the speed of 200~1000 rpm, evaporate the organic solvent, liposomes suspension solution is got, after freeze drying (temperature at -50℃, the degree of vacuum is 50 millitorr), a kind of loose CoQ_{10} –containing preliposomes which contains spongiamine is got.

Example 4: test of stability

Put the three batch of containing spongiamine CoQ_{10} –containing preliposomes and common CoQ_{10} –containing liposomes (the liposomes suspension before drying) separately into the condition which is 40℃ and 75% degree of humidity. After 0, 1, 2 and 3 months, use High Performance Liquid Chromatography (HPLC) to test the content of CoQ_{10} in the preliposomes and the common liposomes, use the content of 0 month CoQ_{10} in the preliposomes and the common liposomes as 100%, compare the content of drug at other time with the above mentioned content of CoQ_{10}, get the percent content of drug as the time goes by.

Table 1 lists the stability comparing result of the content of CoQ_{10} in the preliposomes and the common liposomes.

Table 1

The change percent of the content of CoQ_{10} (%)